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Review

Influence of Interleukin-6 and G174C Polymorphism in IL-6 Gene on Obesity and Energy Balance

K. Popko, E. Gorska, U. Demkow

Department of Laboratory Diagnostics and Clinical Immunology of Developmental Age, Warsaw Medical University, Warsaw, Poland

Abstract
Obesity is a multifactor disease with a very complicated etiology. Genetic factors play an important role in the development of primary obesity. They may be responsible for up to 40% of causes leading to obesity. There are a great number of genes affecting food intake and energy expenditure. Serious consequences accompanying obesity, e.g., type 2 diabetes and lipid abnormalities may be caused by increased level of proinflammatory cytokines, such as IL-1, IL-6, and TNF. It is possible that polymorphisms located in cytokine genes affect the level of protein expression. It is known that IL-6 plays a role in lipid metabolism and energy expenditure. The polymorphism found in point 174 (*G*174C) of a promoter region of IL-6 gene affects the level of interleukin-6 expression and, consequently, may lead to obesity and correlated conditions.

Key words: obesity, gene polymorphism, IL-6

Biological Functions of Interleukin-6

For many years biological function of interleukin-6 (IL-6), historically known as interferon beta-2 (IFN-β-2) or B cell stimulatory factor-2, was limited to stimulation of B cell proliferation. Protein molecular structure analysis and gene expression studies led to the detailed assessment of IL-6 expression and localization in the organism [1].

Recent studies have shown that up to 30% of IL-6 in the blood stream is secreted by adipose tissue, and the cytokine level positively correlates with body mass index (BMI) [2, 3]. Intraperitoneal adipocytes secrete three times more IL-6 than subcutaneous adipose tissue [4]. The published data suggests that the amount of cytokine secreted by adipocytes is related to their size and fat content. Resting adipocytes are able to secrete IL-6, but its expression significantly increases in consequence of glucocorticosteroid or catecholamine activity. TNF secretion is able to induce a 60-folds increase in IL-6 production [5].

IL-6 is one of major proinflammatory cytokines responsible for immune response activation. Its pleiotropic activity includes the induction of acute phase proteins secretion by liver cells, B-cell differentiation into plasma cells, T-cells activation, and T cells differentiation into cytotoxic cells. It is observed that in mixed lymphocyte culture (MLC) IL-6 is able to induce a 100-fold increase in the number of cytotoxic T cells. IL-6, synergically with other cytokines, such as IL-3, influences hematopoiesis and platelets formation in bone marrow by the activation of proliferation and differentiation of various hematopoietic lineages stem cells, e.g., megakariocytes, granulocytes, and macrophages [1, 6]. Moreover, it exerts strong effects on hormonal balance and may induce some endocrinological disturbances. It is suggested that IL-6 may affect the increase of free fatty acids level. IL-6 concentration is elevated in patients with lipid disorders and insulin resistance [7]. Various effects of IL-6 on biochemical parameters are related to IL-6 concentration, determined by IL-6 gene polymorphisms, influencing both encoding sequence and promoter region.

Some authors suggest that IL-6 can be responsible for the development of several pathophysiological states. A few studies showed that IL-6 is able to induce mesangial cells proliferation in mesangial nephritis. Additionally, increased serum concentration of IL-6 is observed in synovial fluid of rheumatoid arthritis patients [8]. Moreover, IL-6 is able to stimulate proliferation of multiple myeloma cells, which suggests the involvement of this cytokine in the pathogenesis of some neoplasms in humans [9, 10]. As a result of these observations, IL-6 antagonists have been developed for clinical use.

IL-6 Gene and Protein Structure

Human IL-6 gene is located on the 7 chromosome at 7p21-p14, between D7S135 and D7S370 [11]. It consists of 5 exons and is 5kb long [12]. IL-6 gene promoter includes numerous regulatory sites allowing the induction of gene expression, e.g., by glucocorticosteroids and cAMP [13, 14]. An extremely important regulatory site binds NF-κB, and is responsible for the induction of IL-6 expression by IL-1 and TNF, mainly in non-lymphoid cells [15, 16]. Both in the encoding sequence and the promoter, numerous single nucleotide polymorphisms (SNP) were found. One of the most commonly found and analyzed polymorphisms are C (cytosine) to G (guanine) transition at position -174 of the promoter.

IL-6 encoding sequence expression leads to the secretion of a 212 amino acid protein. As a consequence of posttranslational modifications, the protein is shortened and its mature form consists of 185 amino acids and contains two glycosylation sites: at positions -73 and -172. It has been shown that monocytes, one

of the major IL-6 producers, are able to secrete five different molecular forms of the cytokine (21.5 to 28 kDa). The isoforms result from posttranslational modifications of precursor proteins including glycosylation and phosphorylation [17-19].

IL-6 Receptor

IL-6 receptor is an 80 kDa glycosylated protein that consists of 449 amino acids. It is also known as CD 126 molecule. The receptor is synthesized as a 468-amino acid length precursor molecule. Its molecular structure is similar to the other cytokine receptors such as M-CSF, PDGF, or IL-11. It contains immunoglobulin-like region in the extracellular domain. The intracellular domain consists of approximately 82 amino acids and is not homologous with other receptors. Two isoforms of the receptor, having various affinity to IL-6 molecules, depending on their concentration (10^{-9} and 10^{-11} M) are identified. IL-6 biological activity is observed at the concentration of 10^{-13}-10^{-15} M, which suggests the presence of the other isoform of the receptor, or at least a high affinity subunit of the receptor. IL-6 receptor transduces the signal through protein kinase C and adenylate cyclase [20, 21]. It has been demonstrated that IL-6, together with other cytokines from the same cytokine family, induces signal transduction though the activation of JAK tyrosine kinases [22]. IL-6 binding to the receptor leads to the homodimerization of a transmembrane glycoprotein (gp130) and the activation of tyrosine kinases JAK1, JAK2, Tyk2, STAT1, and STAT3 that induce signal transduction pathways [23]. Additionally, the presence of a soluble IL-6 receptor interfering with gp130 has been demonstrated. The soluble receptor plausibly regulates cytokine activity through the inhibition of IL-6 binding to the surface receptor and also, it can serve as a carrier protein [24].

Influence of G174C Polymorphism on Energy Balance

Recent studies concentrate on the influence of IL-6 gene polymorphisms on the development of certain medical conditions. The relation between some genetic variant and the development of obesity seems to be more and more precisely documented.

IL-6 expression is regulated by various factors. IL-1 and TNF induce the expression of IL-6. That explains an increased level of IL-6 in chronic inflammatory diseases, such as rheumatoid arthritis. On the other hand, steroid hormones such as estradiol or glucocorticosteroids, inhibit IL-6 transcription [25], which is observed in postmenopausal women and may be related to the development of osteoporosis. G/G genotype in G174C polymorphic site of the IL-6 gene promoter region correlates with increased IL-6 concentration and leads to increases in CRP and the bone resorption marker sCTx (serum C-telopeptide cross-link of type 1 collagen) [26].

The influence of G174C polymorphism on the process of energy expenditure may underlie the role of IL-6 in the development of obesity and type 2 diabetes. Kubaszek et al [27] have shown that the subject bearing C/C genotype are more resistant to insulin and have higher serum glucose concentration. They also have a lower level of energy expenditure and a slightly higher BMI compared with subjects bearing G allele.

The influence of G174C polymorphism on the process of energy expenditure can be explained by various mechanisms. The process is regulated centrally by IL-6 expression in the hypothalamus. *In vitro* studies have shown that mice bearing inactive IL-6 gene, after central, but not peripheral, administration of exogenous IL-6, increase energy expenditure [28]. In humans, high level of cytokines (including IL-6) and the synthesis of cytokines in brain lead to an increase in resting energy expenditure and may cause cachexy [29]. Peripheral administration of IL-6 causes a dose-dependent increase in resting metabolism and the activity of hypothalamus-pituitary gland-suprarenal gland axis, suggesting that corticotropin releasing hormone is intermediary in both processes [30]. Adrenergic stimulation can also be a mechanism of IL-6 action in the process of energy expenditure. IL-6 causes heart rate acceleration, norepinephrine level increase and sympathetic nervous system stimulation, all being efferent regulators of energy expenditure [31-33]. Moreover, sympathetic neurons express both IL-6 and IL-6 receptor; hence they are sensitive to IL-6 activity [34]. In renal cancer patients, administration of IL-6 leads to increases in norepinephrine and resting energy expenditure [35].

Another hypothesis includes the possibility of correlation between IL-6 and leptin activities. Animal studies have shown that IL-6 knockout mice are obese and, despite a relatively high leptin level, are insensitive to its effects [28]. Leptin effects on the energy expenditure process are mediated by corticotropin releasing factor that increases energy expenditure and stimulates sympathetic nervous system in rats. Similarly, in humans, exogenous leptin administration increases energy expenditure [36].

The influence of IL-6 on the regulation of body mass can be connected with the fact that leptin blood level is significantly increased after physical exertion and achieves the maximum value in the final stage of exercise [37]. Moreover, skeletal muscles are the main source of IL-6 produced in response to the increased physical exertion [38]. In addition to muscles, other organs, such as brain or adipose tissue, increase the secretion of IL-6 after physical exertion [39-41]. Numerous studies have demonstrated the increase of IL-6 production in skeletal muscles and its increase in serum in response to physical exertion [8, 42]. Transcriptional activity of IL-6 in muscles is regulated not only by the intensity of physical exertion, but also inversely depends on the glycogen content in active muscles [43]. Administration of carbohydrates during physical exertion results in a decrease of IL-6 serum concentration, but does not change the gene expression level [43]. It is suggested that glucose exerts its action at a posttranslational level, inhibiting cytokine transport.

Some authors also suggest that IL-6 works as a hormone, and that is why it exerts its biological actions during physical exertion. According to this hypothesis,

IL-6 is secreted by active muscles as a hormonal signal to liver or adipose tissue to activate glycogenolysis or lipolysis [38]. Helge et al [44] have demonstrated a positive correlation between IL-6 secretion and glucose absorption. It is also possible that IL-6 serves as an indicator of carbohydrates availability. A similar relation has been found regarding the influence of physical exertion on adipose tissue metabolism in the studies in which both IL-6 mRNA expression and the cytokine's level increase. However, carbohydrates administration during physical exertion leads to inhibition of IL-6 mRNA expression [45]. That indicates that there are other regulatory pathways for IL-6 expression in muscles and adipose tissue.

Alleles connected with decreased IL-6 expression can be responsible for the low cytokine's secretion during physical exertion, which can to low level of metabolism, decreased fat burning, and, in consequence, obesity. Recently, the influence of IL-6 on human metabolism is broadly discussed. A connection between IL-6 and carbohydrate or lipid metabolism suggests the cytokine's involvement in the development of obesity and type 2 diabetes. All regulatory functions seem to be related to the cytokine secretion in various tissues in response to external and internal triggers. IL-6 activity can be exerted locally or systemically.

Many authors consider type 2 diabetes and insulin resistance as a symptom of inflammatory response in the organism [7]. The hypothesis can be confirmed by the observation of high levels of acute phase proteins such as CRP, amyloid A, alpha-1-acid glycoprotein, sialic acid, and cortisone in diabetic patients [46, 47]. Moreover, a significant increase in proinflammatory cytokines levels is found in obese population. The increase in IL-6 level, in parallel to increased glucose and insulin concentrations, suggests a possible involvement of the cytokine in glucose metabolism, especially in adipocytes. It is unclear which allele in *G*174C polymorphic site of IL-6 gene promoter predisposes to the development of type 2 diabetes. Nevertheless, Vozarova et al [48] have demonstrated that allele G may be responsible for high susceptibility to type 2 diabetes. On the other hand, the study performed by Mohling et al [49] in the German population has shown the increased probability of type 2 diabetes development in C/C allele carriers. Additionally, studies performed in the Finnish population failed to show any direct relation between polymorphisms and susceptibility to diabetes. However, it has been demonstrated that C/C genotype significantly increases the risk of diabetes in patients with the diagnosis of glucose intolerance, carrying allele A in the *G*308A polymorphic site in the promoter region of TNF gene [50]. Taken together, data suggest an indirect relation between the genotype and risk of type 2 diabetes.

In non-diabetic subjects, there is a relation between C/C genotype and low fasting insulin level and sensitivity to insulin. At the same time, there is a relation between C/C genotype and lower serum IL-6 level [50]. In this case, white blood count was an additional marker of peripheral IL-6 activity; the count being significantly lower in subjects bearing C/C genotype compared with allele G carriers.

Illig et al [51] have shown a connection between allele G and high risk of type 2 diabetes. Moreover, the authors showed increased levels of MCP-1/CCL-2 in sera obtained from the C/C genotype bearing patients. It is well established that increased levels of MCP-1 correlate with a low risk for diabetes. MCP-1 seems a potential factor connecting *G*174C polymorphism with the susceptibility to diabetes. This connection is seen only in normal weight or slightly overweight males. Similar relations have not been found in females or obese males, which suggests the influence of obesity and hormonal factors in the development of type 2 diabetes. No correlation between *G*174C polymorphism in IL-6 gene promoter and the development of insulin resistance has been evidenced. The relation between *G*176C polymorphism and obesity has also been analyzed in obese children, but results are inconclusive [52].

Confusing data obtained by authors studying the influence of *G*174C polymorphism on the incidence of diabetes and insulin resistance might be explained by difficulties in selection of control and study groups. Type 2 diabetes development depends on numerous factors significantly modulating the risk of disease diagnosis. Apart from various genetic factors, numerous other conditions, such as obesity, glucose tolerance, sex, age, lifestyle, and dietetic habits may influence diabetic status of the patient. This is why a careful selection of analyzed groups seems to be extremely important. As there are so many divergences and uncertainties, there is an urgent need to study associations between polymorphisms of genes encoding proinflammatory cytokine genes and various type 2 diabetes risk factors.

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Address for correspondence:
Katarzyna Popko
24, Marszalkowska St.
00-576 Warsaw
Poland
Phone/fax: +48 22 6296517
E-mail: aksiak@interia.pl